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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

SCHMIDT, M

ART UNIT

PAPER NUMBER

1635

DATE MAILED:

09/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/068,751

Applicant(s)

Franz et al.

Examiner

Schmidt

Group Art Unit

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—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-19 is/are pending in the application.
Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-3 is/are rejected.
- ☒ Claim(s) 4-19 is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

- ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____.

Attachment(s)

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ ☐ Interview Summary, PTO-413
- ☒ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other _____

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DETAILED ACTION

1. Claims 4-19 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention recites a “nucleic acid working model” which is not considered statutory subject matter because it is not clear whether the “working model” as claimed is drawn to a therapeutic *method* comprising a nucleic acid construct or a *composition of matter* (the nucleic acid construct) for use in treatment.

Claim Rejections - 35 USC § 112

3. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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It is not clear what the language “nucleic acid working model” in claims 1-3 refers to. The “working model” could refer to a therapeutic *method* comprising a nucleic acid construct or a *composition of matter* (the nucleic acid construct) for use in treatment.

In claim 1 it is not clear whether “the nucleic acid” refers to the “gene therapeutic nucleic acid” or the “regulatory nucleic acid.”

In claim 1, it appears that the word “ribosome” is incorrect and should read “ribozyme.”

It is not clear if applicants in claim 2 intend to refer to “particularly humans” or to “mainly from rats” as the preferred embodiment.

It is not clear whether applicants in claim 3 intend to refer to the various ranges as having varying degrees of preferred embodiments, and if so, what the hierarchy is in view of the language “comprises,” “*above all...up to... -1600,*” “*especially from... up to...-1800,*” “*above all... up to... -2100*” and “*or from... up to -2700.*”

In dependent claims 2-3 the indefinite article “A” is used to define the scope of the preamble of the claim. However, since the claims are dependent, use of the definite article “The” would more clearly define the scope of the preamble of the claim as well as be grammatically correct.

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4. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For the purposes of this rejection and in view of the 35U.S.C 101 and 112 rejections, “working model” is interpreted as a method of gene therapy via antisense or ribozyme application.

The claims are drawn to a nucleic acid “working model” containing a 5' myosin light chain 2 gene (MLC2) promoter for expression of a therapeutic gene product such as an antisense or ribozyme. Claim 2 specifies the MLC2 regulatory region from mammalian hearts, particularly humans or rodents (rats). Claim 3 specifies promoter regions from the MLC2 gene for use upstream of the therapeutic gene.

The specification as filed teaches construction of vector constructs and recombinant adenovirus constructs containing an MLC2-luciferase sequence. *In vitro* studies of Adenovirus MLC2-luciferase expression levels in A10- (rat smooth muscle cell line), N9c2-(rat heart myoblast cell line), HeLa- (human cervix carcinoma cell line), 293, and primary neonatal rat cardiomyocyte cells were shown. Specifically, the specification teaches “the MLC2 promoter in neonatal cardiomyocytes is active, while the expected activity of the smmhc (negative control, for expression only in smooth muscle cells) promoter in neonatal and adult smooth muscle cells was missing.” The adenovirus constructs were further applied via injection to neonatal rat left heart cavities and for comparison to upper thigh muscle. Expression of the Ad-mlcLuc was shown as specifically active in heart and not in skeletal muscle.

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The claims as written read on therapeutic application of antisense and ribozyme -MLC-2-fusion products. No context is given for the therapeutic application and therefore read on whole organism application.

There is a high level of unpredictability known in the gene therapy art as well as the antisense/ribozyme art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Anderson, who teaches the unpredictability of the gene therapy based on "poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (p.30)."

One of skill in the art would not accept on its face the successful delivery of just any antisense or ribozyme *in vivo* in view of the lack of specific guidance in the specification and the unpredictability in the art (see Crooke p3, lines 5-10). Specifically, although the specification teaches AdenovirusMLC-2luciferase expression after injection, this application does not correlate with application of any antisense/ribozyme or other gene products from the same construct. The specification does not teach (1) stability of an antisense molecule *in vivo*, (2) effective delivery to

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the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of "trial and error" experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

5. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For the purposes of this rejection and in view of the 35U.S.C. 101 and 35U.S.C. 112 rejections, "working model" is interpreted as a nucleic acid construct comprising the MLC2 promoter linked to a sequence encoding an antisense or ribozyme for use in therapeutic applications. However, in light of the indefiniteness of the language "working model" the structure of the claimed invention is not clear and further, the breadth of the genus claimed is not clearly described and therefore no determination of the extent of claimed "representative number of species" can be properly ascertained.

For description of the claimed MLC-2/antisense or ribozyme encoding constructs, there is a high degree of unpredictability in the art as shown *supra*, specifically, (1) for accurate targeting of antisense/ribozymes to the gene of interest and (2) for any whole organism application of

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antisense molecules (or any such gene therapy associated sequences). The specification as filed only teaches MLC-2/luciferase expression and not specific constructs for MLC-2 directed antisense/ribozyme or other therapeutic gene coding sequence expression. There is no correlation between application of luciferase and application of antisense/ribozyme or other gene therapy sequences for therapeutic application (as interpreted by the language of the claims, "therapeutically effective product") because of the unpredictability of the art. Therefore, the specification as filed does not disclose sufficient relevant identifying characteristics such as structure, physical and chemical characteristics, or functional characteristics of MLC-2/antisense, ribozyme, or other therapeutically applicable sequences to allow one skilled in the art possession of the invention as claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following in the alternative: Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al. in view of Ricigliano et al. and Zaia et al.

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The claims are drawn to a nucleic acid “working model” containing a 5' myosin light chain 2 gene (MLC2) promoter for expression of a therapeutic gene product such as an antisense or ribozyme. Claim 2 specifies the MLC2 regulatory region from mammalian hearts, particularly humans or rodents (rats). Claim 3 specifies promoter regions from the MLC2 gene for use upstream of the therapeutic gene ranging from (+18 to -19) to one of the following: -800, -1600, -1800, -2100, or -2700. For the purposes of this rejection and in view of the 35U.S.C. 101 and 35U.S.C. 112 rejections, “working model” is interpreted as a nucleic acid construct comprising the MLC2 promoter linked to a sequence encoding an antisense or ribozyme for use in therapeutic applications.

Franz et al. teach “a model system for selective targeting of genes to the heart of transgenic mice” where “a 2.1kB fragment of the 5' flanking region of the rat cardiac MLC-2 gene was fused to the firefly luciferase reporter gene and introduced into fertilized mouse oocytes (abstract).” The 2.1kB MLC-2 fragment extends from +12 to -2700 (P.630). Specific regulatory regions of the promoter were taught on pages 635-636. Franz et al. also teaches application of the model system “for selective targeting of foreign gene products to the ventricular myocardium (p. 637).” Franz et al. does not teach use of this expression construct for expression of antisense or ribozyme sequences per se.

Arnold et al. teach application of a chicken MLC-2A promoter- chloramphenicol acetyl transferase fusion construct for expression in primary cultures of chicken muscle. Arnold et al. does not teach use of this expression construct for expression of ribozyme sequences per se.

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Knowlton et al. teach expression of rat MLC-2 luciferase fusion constructs in neonatal rat ventricular cells. Knowlton et al. does not teach use of this expression construct for expression of ribozyme sequences per se.

Shubeita et al. teach expression of an MLC-2 promoter-luciferase fusion construct in neonatal rat ventricular myocytes. Shubeita et al. does not teach use of this expression construct for expression of antisense or ribozyme sequences per se.

Navankasattusas et al. teach identification of a “a 250-bp fragment of the MLC-2 5' flanking region which can confer cardiac muscle-specific expression. Within this MLC-2 promoter fragment lies a 28-bp conserved regulatory element (HF-1), which confers muscle specificity in transient assays in primary ventricular muscle cells.” (P. 1469, column2) They further define important regions in the MLC-2 promoter by studying the affect of point mutations in the region using a luciferase reporter construct. They teach “in the native 250-bp MLC-2 promoter fragment, mutations in the single E-box had little effect on cardiac muscle specificity, while point mutations in either the HF-1a or HF-1b binding site significantly reduced promoter activity, underscoring the importance of both the HF-1a and HF-1b sites in the transcriptional activation of this cardiac muscle gene.” (P. 1470, column 1, lines 8-17) Navankasattusas et al. does not teach use of this expression construct for expression of antisense or ribozyme sequences per se.

Thornburn et al. teach a MLC-2 luciferase fusion construct for study of the activation of MLC-2 by Raf-1 kinase. Thornburn et al. does not teach use of this expression construct for expression of antisense or ribozyme sequences per se.

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Goswami et al. teach “the cardiac MLC-2 gene contains several conserved sequences in the proximal promoter, which includes an A/T rich sequence, TTATTTTTA (element B), that is similar to the MEF-2 binding site... element B is responsible for the serum-induced activation of the MLC-2 promoter in cardiac muscle cells... The cardiac tissue-restricted expression of MLC-2 is also mediated by a negative element (CSS), located upstream (-371 to -282) that represses the promoter activity in skeletal muscle cells...” (P. 200) They teach an MLC-2 -CAT fusion construct but do not teach use of this expression construct for expression of antisense or ribozyme per se.

Ricigliano et al. teach a DNA construct comprising muscle specific regulatory elements, such as a promoter and a DNA sequence under control of the promoter, such as an antisense, for therapeutic (immunization or gene therapy) application to muscle genes affected by a muscle disease (abstract).

Zaia et al. teach ribozymes as a “second generation” of antisense (p. 101).

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to make a nucleic acid construct comprising an antisense sequence under control of a muscle tissue specific promoter as taught by Ricigliano et al. specifically under control of the MLC-2 promoter taught by Franz et al., Arnold et al., Knowlton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al.

One of ordinary skill in the art would have been motivated to make a muscle specific expression construct comprising a muscle specific promoter fused to a sequence encoding antisense for “blocking an abnormal muscle gene” as taught by Ricigliano and likewise for a

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ribozyme, a functionally equivalent, "second generation" antisense as taught by Zaia et al. One of ordinary skill in the art would have been further motivated to have substituted the muscle specific promoters taught by Ricigliano et al. with the MLC-2 promoter as taught by Franz et al., Arnold et al., Knowlton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al. for selective gene expression in cardiac myocytes as taught by Franz et al. (abstract).

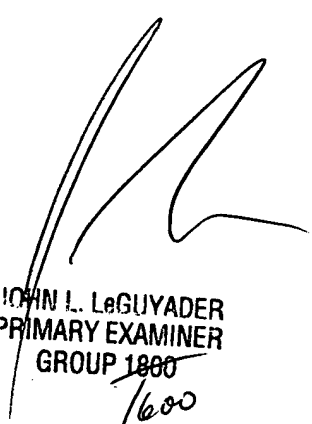
One of ordinary skill in the art would have had a reasonable expectation of success for cardiac specific expression of an antisense molecule from the MLC-2 promoter because Ricigliano et al. broadly teaches use of tissue-specific promoters, like MLC-2, to heterologously express antisense, and functionally equivalent ribozymes.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.


JOHN L. LeGUYADER
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1600